REMARKS/ARGUMENTS

Favorable consideration of this application in light of the following discussion is respectfully requested.

Claims 1-48 are pending in the application.

In the outstanding Office Action, Claim 29 was objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim; Claims 1-3, 13, 28-29, 31, 33-35, 37, 43-44 and 46-48 were rejected under 35 U.S.C. § 102(b) as being anticipate by Dromey; Claims 1-3, 10, 12-13, 15-16, 23, 25-26, 28-31, 33-35, 37, 43-44 and 46-48 were rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Hines; Claims 14, 27, 32 and 45-46 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Hines as applied to Claims 1, 15, 28 and 34 above, and further in view of Yates (*Analytical Chemistry* 1995, 67, 1426-1436); Claims 5, 11, 18, 24, 41-42 and 46 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Hines as applied to Claims 3, 10, 16, 23, 37 and 40 above, and further in view of Kwok; Claims 4, 6-9, 17, 19-22, 36 and 38-39 were indicated as allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicants gratefully acknowledge the indication of the allowable subject matter.

Applicants acknowledge with appreciation the personal interview between the Examiner, the inventor, and Applicants' representative on March 24, 2005. During the interview, the Examiner agreed that the disclosed invention is different from that taught in the applied references. Regarding the claimed invention, the Examiner acknowledged the explanations provided and indicated that such arguments are likely to prove to be persuasive once formally filed.

Applicants again traverse the objection to Claim 29 under 37 C.F.R. § 1.75(c). Applicants submit that by reciting that the mass spectra recited in Claim 28 is mass spectra

obtained by any one of dissociation and full-scan, Applicants have further limited the mass spectra from mass spectra obtained by means other than dissociation or full-scan.

Briefly recapitulating, Claim 1 is directed to a method for mining mass spectra. The method includes a) specifying spectral characteristics of the mass spectra to mine; b) specifying a relationship between the spectral characteristics; c) searching the mass spectra for portions of the mass spectra which match the spectral characteristics based on the relationship; and d) assigning scores to the portions of the mass spectra to indicate a degree of correlation between the portions of the mass spectra and the spectral characteristics. Applicants' claimed method enables detection of tandem mass spectra data that corresponds to various peptide forms.[1] That is, conventional use of mass spectral data to predict chemical structures and even peptide sequences is well-described in the prior art. However, Applicants' claimed inventions do not predict structures or sequences from MS data. Rather, Applicants' claimed inventions identify data that displays specific characteristics ***defined by the user***. These characteristics include hierarchically defined combinations of loss ions, product ions and ion series. Independent Claims 15, 28, 33, 34, 46, and 47 are directed to alternative embodiments, each identifying data that displays specific characteristics ***defined by the user*** and including hierarchically defined combinations of loss ions, product ions, and ion series.

Dromey describes the identification of chemical structure or structural class from features of a mass spectrum.[2] Features in the spectrum of an unknown compound are used to calculate a "series displacement index" (SDI), which is used to search a table of SDI values for known chemical structures. This includes calculation of the SDI.[3] Dromey uses a reference set of spectral peaks based on an alkane ion fragmentation reference series: 41, 55,

[1] Specification, page 2, lines 32-33.
[2] Dromey R. (1976) Anal. Chem. 48: 1464-1469
[3] Dromey, p. 1465, column 1, lines 12-49 and column 2 , lines 1-10 and Figure 1

69, 83...[4] and then calculates the SDI from mass differences between the actual spectrum peaks and the reference peaks and from the normalized intensities of the actual peaks.[5] In contrast, Applicants' claimed method scores certain product ion(s), loss ion(s) and/or ion series that correspond to values for these parameters specified by the user, rather than in relation to a reference ion series. The claimed scoring method combines any user-specified combination of product ion(s), loss ion(s) and ion series(s), whereas the Dromey approach only scores ions in relation to the reference ion series. Moreover, Applicants' claimed scoring allows specification of a conditional hierarchy, in which certain product ions, loss ions and/or ion series are scored only if certain other specified features are present. Dromey imposes a much simpler, less flexible restriction on selection of ions to scored, through use of the d_m relationship term.[6] Thus, Dromey does not disclose or suggest Applicants' claimed sequence of a) specifying spectral characteristics; b) specifying a relationship; c) searching the mass spectra for portions of the mass spectra which match the spectral characteristics based on the relationship; and d) assigning scores.

Hines describes a method for *de novo* identification of sequences from tandem mass spectra of peptides.[7] A peak detection routine generates a list of peaks and peak intensities from a spectrum. Hines describes a "transformation" step[8] in which the algorithm selects the most abundant ion from the peak list (a "seed ion") and generates an "ion family" (Figure 1) using generic formulae and structures for different ion types (listed in Table 1). The matching of predicted ion families to spectral peaks and the linking of ion families to establish sequence-related ion series enables sequence identifications.[9] The selection of peaks to score (i.e., the transformation step) is driven entirely by selection of the seed ion and

[4] Dromey, p. 1465, line 20 and illustrated in Figure 1
[5] Dromey, eq 1, p. 1465 and example calculation on lines 1-3, Column 2, p. 1465.
[6] Dromey, p. 1465, column 1, line 18
[7] Hines, W. M. et al. (1992) J. Am. Soc. Mass Spectrom. 3: 326-336
[8] Hines, p. 329, column 1, line 10
[9] Hines, p. 330, paragraphs 1-2.

the rules defined for peptide fragment ion families (Table 1 and Figure 1), because the sole purpose of the Hines algorithm is peptide sequence analysis.

In contrast, Applicants' claimed method enables complete flexibility in the specification of spectral features to score (e.g., any combination of product ion(s), loss ion(s) and/or ion series). This is because selection of product ion(s), loss ion(s) and/or ion series is not strictly dictated by the rules of peptide ion fragmentation chemistry and instead may be dictated by the features of any chemical substance of interest. In the transformation step described by Hines, only signals that fit prescribed ion family relationships to the seed ion are considered. In Applicants' claimed method for scoring ion series, all peaks in the spectrum are considered (Figures 6 D and 6H of our application) as possible members of the series. Thus, Applicants' claimed method first aligns the user-specified ion series with the highest *m/z* ion in the spectrum, then with the next highest, etc., until all alignments have been evaluated and then selects the best score (Figure 6D of Applicants' application).

MPEP § 2131 notes that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art." *Brown v. 3M*, 265 F.3d 1349, 1351, 60 USPQ2d 1375, 1376 (Fed. Cir. 2001) (claim to a system for setting a computer clock to an offset time to address the Year 2000 (Y2K) problem, applicable to records with year date data in "at least one of two-digit, three-digit, or four-digit" representations, was held anticipated by a system that offsets year dates in only two-digit formats). See also MPEP § 2131.02. "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236,

9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Because Dromey and Hines do not disclose or suggest all the features recited in Applicants' independent claims, Dromey and Hines do not anticipate the invention recited in Applicants' independent claims, and all claims depending therefrom.

Applicants have considered the Yates disclosure and submit that Yates does not cure the deficiencies of Hines of Dromey. Yates describes a method for identifying modified peptide sequences by correlation of uninterpreted tandem mass spectra with database sequences.[10] To identify a modified sequence, the user must specifying an amino acid-specific mass modification (e.g., phosphorylation (+80 Da) on Ser) of interest. The search algorithm then selects peptide sequences containing the specified amino acid with the specified modification.[11] Those sequences with a mass equal to the precursor ion mass for the MS-MS spectrum and then further subjected to preliminary scoring and cross-correlation comparisons and these scores are used to rank the matched sequences. Both the preliminary scoring and cross correlation steps compare theoretical peaks corresponding to the candidate sequences with real *m/z* signals in the MS-MS spectrum under evaluation (see Eng et al. (J. Am. Soc. Mass Spectrom. (1994) 5: 976-989). Only signals that correspond to peptide bond fragmentations are considered and only *m/z* signals that match the theoretical values are scored. In Applicants' claimed invention, product ions and loss ions may be specified by the user and scored. The Yates algorithm scores only those product ions resulting from predicted peptide bond fragmentations and does not score any loss ions. Moreover, Applicants' claimed scoring of ion series scores m/z peaks in the specified relationship to each other, regardless of their absolute positions on the m/z axis. MS-MS spectra of peptides with different mass modifications share sets of signals whose relative spacing on the m/z is fixed, but whose absolute positions depend on the mass of the modification. Thus, the Yates

[10] Yates, J.R. et al. (1995) Anal. Chem. 67: 1426-1436
[11] Yates, Figure 1 and 3rd paragraph, p. 1429

algorithm only allows detection of modifications whose mass and amino acid specificity can be detected beforehand, whereas our method detects spectra of sequences bearing any modification.

Furthermore, the Official Action states that "the searching algorithm is used to modify the mass spectrometer's acquisition parameters from a neutral loss scan to a product ion MS/MS scan as found on p. 1428 in the first full paragraph. Applicants traverse this finding. The results of the search algorithm are not used to control the instrument. Instead, the switch to product ion MS/MS scan was instead triggered when ion current for the specified neutral loss (-49 from the doubly charged precursor ion) exceeded a threshold value of 50,000 counts.[12] In contrast, Claims 14, 27 and 32 specify using the scores from our algorithm to adjust the control parameters of the device based on the scores.

Applicants have also considered the Kwok reference and submit Kwok does not cure the deficiencies of Hines. Kwok describes a method to extract information from the mass spectrum of an unknown compound and search the information against similarly extracted information for a library of spectra for known compounds.[13] Kwok describes nine different spectral data classes, including ion series, characteristic ions, neutral losses and others (Table 1). The ion series specified by Kwok are not user-defined, as in Applicants' claimed invention, but instead represent specifically defined series reflecting certain structures (e.g., "...*m/e* 15, 29, 43, 57, 71, 85 and 99...").[14] Other ion types, such as "characteristic ions" and "fingerprint ions" (Table 1) are defined not by any rational chemical considerations, but instead as the most abundant odd- and even-mass ions falling within certain mass ranges in the spectrum.[15] Applicants' claimed invention specifies no such ion types.

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[12] Yates, p. 1428, first complete paragraph
[13] Kwok, K.S. et al. (1973) J. Am. Chem. Soc. 95: 4185-4194
[14] Kwok, p. 4186, last line and p. 4187, first line
[15] Kwok, p. 4188, first full paragraph and fifth paragraph

Also, as noted previously, the Hines algorithm is based on defined relationships of ion series in peptide MS-MS spectra and does not include neutral losses or product ions as recited in Applicants' Claim 5 and as disclosed in Kwok. Hines failure to disclose relationships of neutral losses or product ions renders the combination of Hines and Kwok incomplete as compared to Applicants' claimed invention.

The Official Action also suggests that it would have been obvious to "incorporate the different types of ions taught by Kwok into the device and method of Hines because of their ability to provide information in the characterization of unknowns as taught by Kwok". Careful examination of the Hines algorithm (see above) shows that these different ion types cannot be incorporated as the Official Action suggests. The ion types considered in the Hines algorithm are only those corresponding to peptide-specific fragmentations (see Table 1 and Figure 1 of Hines). Because the transformation and linking steps in Hines are dictated by these rules for generating ion families (Hines, p. 329, 2nd paragraph), other ion types, particularly those not explicitly related to peptide fragmentation have no place in the calculation.

In addition, Applicants traverse the suggestion that incorporating the features described by Kwok into the de novo sequencing algorithm of Hines would be obvious. Applicants submit the combining of these different types of parameters for peptide sequencing has not been done despite the development of several de novo sequencing programs over the past 10 years. Furthermore, Applicants submit there is no teaching, suggestion, or motivation, either explicitly or implicitly, in either reference to combine the algorithm of Hines with the searching of Kwok to arrive at Applicants' inventions recited in Claims 5, 11, 18, 24, 41-42 and 46. Thus, for each of the previous reasons, Applicants submit the outstanding rejection of Claims 5, 11, 18, 24, 41-42 and 46 under 35 U.S.C. § 103(a) is an impermissible hindsight reconstruction of Applicants' invention.

As none of the cited prior art, individually or in combination, disclose or suggest all the elements of independent Claim 1, Applicants submit the inventions defined by Claim 1, and all claims depending therefrom, are not rendered obvious by the asserted prior art for at least the reasons stated above.[16] Applicants submit the inventions recited in independent Claims 15, 28, 33, 34, 46, and 47 for substantially similar reasons.

The present amendment is submitted in accordance with 37 C.F.R. § 1.116 which permits amendments placing the claims in better form for consideration on appeal after final rejection. Since the present amendment clarifies the claimed invention, it is respectively requested that 37 C.F.R. § 1.116 be liberally construed and the present amendment be entered.

Finally, paragraph 10 of the Official Action states that "...the claims are generic in nature and include situations in which a database is examined to match an experimental spectra with a known spectra or features of a known spectra..." At least for the preceding reasons and for the reasons discussed during the personal interview, Applicants traverse this assertion. As discussed throughout the prosecution of this application, Applicants' invention is directed toward mining data, not mining of databases or libraries as performed Dromey, Yates and Kwok.

[16] MPEP § 2142 "...the prior art reference (or references when combined) must teach or suggest **all** the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

Accordingly, in light of the previous discussion, Applicants respectfully submit that the present application is in condition for allowance and respectfully request an early and favorable action to that effect.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Eckhard H. Kuesters
Attorney of Record
Registration No. 28,870
Michael E. Monaco
Registration No. 52,041

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 08/03)
EHK/MEMO/kkn

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